General

Guideline Title

Cirrhosis in over 16s: assessment and management.

Bibliographic Source(s)

National Guideline Centre. Cirrhosis in over 16s: assessment and management. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jul 6. 14 p. (NICE guideline; no. 50).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- May 12, 2016 – Fluoroquinolone antibacterial drugs : The U.S. Food and Drug Administration (FDA) is advising that the serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with sinusitis, bronchitis, and uncomplicated urinary tract infections who have other treatment options. For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Guideline Centre on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance and related appendices.

The wording used in the recommendations in this guideline (for example words such as 'offer' and 'consider') denotes the certainty with which the recommendation is made (the strength of the recommendation) and is defined at the end of the "Major Recommendations" field.

Diagnosis

Be aware that there is an increased risk of cirrhosis in people who:

- Have hepatitis B virus infection
- Have hepatitis C virus infection
- Misuse alcohol
- Are obese (body mass index [BMI] of 30 kg/m^2 or higher)
- Have type 2 diabetes

Also see the NICE guidelines on alcohol-use disorders: diagnosis and management of physical complications , alcohol-use disorders: prevention , alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence . See the NGC summaries of the NICE guidelines Non-alcoholic fatty liver disease: assessment and management, Type 2 diabetes in adults: management, Obesity: identification, assessment and management, and Hepatitis B (chronic). Diagnosis and management of chronic hepatitis B in children, young people and adults.

Discuss with the person the accuracy, limitations and risks of the different tests for diagnosing cirrhosis.

Offer transient elastography to diagnose cirrhosis for:

- People with hepatitis C virus infection
- Men who drink over 50 units of alcohol per week and women who drink over 35 units of alcohol per week and have done so for several months
- People diagnosed with alcohol-related liver disease

Offer either transient elastography or acoustic radiation force impulse imaging (whichever is available) to diagnose cirrhosis for people with NAFLD and advanced liver fibrosis (as diagnosed by a score of 10.51 or above using the enhanced liver fibrosis [ELF] test). Also see the "Assessment for Advanced Liver Fibrosis in People with NAFLD" section in the NGC summary of the NICE guideline Non-alcoholic fatty liver disease: assessment and management.

Consider liver biopsy to diagnose cirrhosis in people for whom transient elastography is not suitable.

For recommendations on diagnosing cirrhosis in people with hepatitis B virus infection, see the "Assessment of Liver Disease in Secondary Specialist Care" in the NGC summary of the NICE guideline Hepatitis B (chronic). Diagnosis and management of chronic hepatitis B in children, young people and adults.

Do not offer tests to diagnose cirrhosis for people who are obese (BMI of 30 kg/m^2 or higher) or who have type 2 diabetes, unless they have NAFLD and advanced liver fibrosis (as diagnosed by a score of 10.51 or above using the ELF test). Also see the "Assessment for Advanced Liver Fibrosis in People with NAFLD" section in the NGC summary of the NICE guideline Non-alcoholic fatty liver disease: assessment and management.

Ensure that healthcare professionals who perform or interpret non-invasive tests are trained to do so.

Do not use routine laboratory liver blood tests to rule out cirrhosis.

Refer people diagnosed with cirrhosis to a specialist in hepatology.

Offer retesting for cirrhosis every 2 years for:

- People diagnosed with alcohol-related liver disease
- People with hepatitis C virus infection who have not shown a sustained virological response to antiviral therapy
- People with NAFLD and advanced liver fibrosis

For recommendations on reassessing liver disease in hepatitis B virus infection, see the "Assessment of Liver Disease in Secondary Specialist Care" section in the NGC summary of the NICE guideline Hepatitis B (chronic). Diagnosis and management of chronic hepatitis B in children, young people and adults.

Monitoring

Risk of Complications

Refer people who have, or are at high risk of, complications of cirrhosis to a specialist hepatology centre.

Calculate the Model for End-Stage Liver Disease (MELD) score every 6 months for people with compensated cirrhosis.

Consider using a MELD score of 12 or more as an indicator that the person is at high risk of complications of cirrhosis.

Hepatocellular Carcinoma

Offer ultrasound (with or without measurement of serum alpha-fetoprotein) every 6 months as surveillance for hepatocellular carcinoma (HCC) for people with cirrhosis who do not have hepatitis B virus infection.

For people with cirrhosis and hepatitis B virus infection, see the "Surveillance Testing for Hepatocellular Carcinoma (HCC) in Adults With Chronic Hepatitis B" section in the NGC summary of the NICE guideline Hepatitis B (chronic). Diagnosis and management of chronic hepatitis B in children, young people and adults.

Do not offer surveillance for HCC for people who are receiving end of life care.

Oesophageal Varices

After a diagnosis of cirrhosis, offer upper gastrointestinal endoscopy to detect oesophageal varices.

For people in whom no oesophageal varices have been detected, offer surveillance using upper gastrointestinal endoscopy every 3 years.

Managing Complications

Offer endoscopic variceal band ligation for the primary prevention of bleeding for people with cirrhosis who have medium to large oesophageal varices.

Offer prophylactic intravenous antibiotics for people with cirrhosis who have upper gastrointestinal bleeding.

Review intravenous antibiotics prescriptions in line with the prescribing intravenous antimicrobials section in NICE's antimicrobial stewardship guideline.

Consider a transjugular intrahepatic portosystemic shunt for people with cirrhosis who have refractory ascites.

Offer prophylactic oral ciprofloxacin or norfloxacin for people with cirrhosis and ascites with an ascitic protein of 15 g/litre or less, until the ascites has resolved. (At the time of publication [July 2016], neither ciprofloxacin nor norfloxacin had a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.)

Definitions

Strength of Recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group (GDG) makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the GDG is confident that, given the information it has looked at, most people would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

Interventions That Must (or Must Not) Be Used

The GDG usually uses 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally 'must' (or 'must not') is used if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation

The GDG uses 'offer' (and similar words such as 'refer' or 'advise') when confident that, for the vast majority of people, an intervention will do more good than harm, and be cost effective. The GDG uses similar forms of words (for example, 'Do not offer…') when they are confident that an intervention will not be of benefit for most people.

Interventions That Could Be Used

The GDG uses 'consider' when confident that an intervention will do more good than harm for most people, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the person's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the person.

Clinical Algorithm(s)

The following algorithms are provided in the full version of the guideline (see the "Availability of Companion Documents" field):

- Cirrhosis in over 16s: assessment and management
- Cirrhosis in over 16s: primary care pathway

A National Institute for Health and Care Excellence (NICE) Pathway titled "Cirrhosis overview" is also provided on the NICE Web site .

Scope

Disease/Condition(s)

Cirrhosis

Other Disease/Condition(s) Addressed

- Hepatitis B virus infection
- Hepatitis C virus infection

Guideline Category

Diagnosis

Evaluation

Management

Risk Assessment

Treatment

Clinical Specialty

Family Practice

Gastroenterology

Internal Medicine

Preventive Medicine

Intended Users

Advanced Practice Nurses

Health Care Providers

Hospitals

Nurses

Patients

Physician Assistants

Physicians

Guideline Objective(s)

- To offer best practice advice on the diagnosis and management of suspected or confirmed cirrhosis in people aged 16 years or older
- To recommend tools to assess the severity of cirrhosis and give advice on monitoring people with cirrhosis to detect and manage complications early, and referral criteria for tertiary care

Target Population

Adults with cirrhosis that is suspected or confirmed when they are 16 years or older

Interventions and Practices Considered

Diagnosis/Evaluation/Risk Assessment

1. Identification of people who may have risk factors for cirrhosis (e.g., people with hepatitis B or C virus infection, people who misuse alcohol, obese people, and people with type 2 diabetes)
2. Diagnosis of suspected cirrhosis
    - Transient elastography
    - Acoustic radiation force imaging
    - Liver biopsy
    - Liver blood tests (not recommended routinely)
3. Retesting every 2 years

Management/Treatment

1. Referral to hepatology specialist
2. Monitoring people with cirrhosis to detect complications early
    - Monitoring for hepatocellular carcinoma using ultrasound or serum alpha-fetoprotein
    - Upper gastrointestinal endoscopy to detect oesophageal varices
3. Management of complications of cirrhosis
    - Endoscopic variceal band ligation for the primary prevention of bleeding
    - Management of ascites (transjugular intrahepatic portosystemic shunt)
    - Prophylactic antibiotics

Major Outcomes Considered

- Accuracy of diagnostic tests (sensitivity and specificity)
- Occurrence hepatocellular carcinoma/variceal bleeding/spontaneous peritoneal bleeding/bacterial infections
- Mortality/survival, including transplant-free survival
- Length of hospital stay
- Time to discharge from hospital
- Readmission rates
- Health-related quality of life
- Reversal of hepatorenal syndrome or improved renal function

- Adverse events of antibiotics and volume replacement
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Guideline Centre on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance and related appendices.

Developing the Review Questions and Outcomes

Review questions were developed using a PICO framework (patient, intervention, comparison and outcome) for intervention reviews; using a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy; and using population, presence or absence of factors under investigation (for example prognostic factors) and outcomes for prognostic reviews.

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the Guideline Development Group (GDG). The review questions were drafted by the National Guideline Centre technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (see Appendix A). A total of 17 review questions were identified (see Table 1 in the full version of the guideline for the guideline review questions).

Searching for Evidence

Clinical Literature Search

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the NICE guidelines manual (see the "Availability of Companion Documents" field). Databases were searched using relevant medical subject headings, free-text terms and study-type filters where appropriate. Where possible, searches were restricted to articles published in English. Studies published in languages other than English were not reviewed. All searches were conducted in Medline, EMBASE, and The Cochrane Library. All searches were updated on 24 August 2015. No papers published after this date were considered.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking GDG members to highlight any additional studies. Searches were quality assured by a second information scientist before being run. The questions, the study types applied, the databases searched and the years covered can be found in Appendix G.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

During the scoping stage, a search was conducted for guidelines and reports on the Web sites listed below from organisations relevant to the topic.

- Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearinghouse (NGC) (www.guideline.gov)
- National Institute for Health and Care Excellence (NICE) (www.nice.org.uk)
- National Institutes of Health Consensus Development Program (consensus.nih.gov)
- National Health Service (NHS) Evidence Search (www.evidence.nhs.uk)

All references sent by stakeholders were considered. Searching for unpublished literature was not undertaken. The National Guideline Centre and NICE do not have access to drug manufacturers' unpublished clinical trial results, so the clinical evidence considered by the GDG for pharmaceutical interventions may be different from that considered by the Medicines and Healthcare Products Regulatory Agency (MHRA) and European Medicines Agency for the purposes of licensing and safety regulation.

Health Economic Literature Search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to cirrhosis in the NHS Economic Evaluation Database (NHS EED), the Health Technology Assessment database (HTA) and the Health Economic Evaluations Database (HEED) with no date restrictions (NHS EED ceased to be updated after March 2015; HEED was used for searches up to 27 August 2014 but subsequently ceased to be available). Additionally, the search was run on Medline and EMBASE using a health economic filter from 2013 to ensure recent publications that had not yet been indexed by the economic databases were identified. This was supplemented by an additional search that looked for economic papers specifically relating to the modelling of liver disease on Medline, EMBASE, HTA, NHS EED and HEED to ensure no modelling studies were missed. Where possible, searches were restricted to articles published in English. Studies published in languages other than English were not reviewed.

The health economic search strategies are included in Appendix G in the full version of the guideline. All searches were updated on 27 August 2015. No papers published after this date were considered.

Identifying and Analysing Evidence of Effectiveness

Research fellows conducted the following tasks:

- Identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against prespecified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population, and reported on outcomes of interest (review protocols are included in Appendix C)

Inclusion and Exclusion Criteria

The inclusion and exclusion of studies was based on the criteria defined in the review protocols, which can be found in Appendix C. Excluded studies by review question (with the reasons for their exclusion) are listed in Appendix L. The GDG was consulted about any uncertainty regarding inclusion or exclusion.

The key population inclusion criterion was:

- Adults and young people (16 years and over) with cirrhosis

The key population exclusion criterion was:

- Children <16 years with cirrhosis

Conference abstracts were not automatically excluded from any review. The abstracts were initially assessed against the inclusion criteria for the review question and further processed when a full publication was not available for that review question. If the abstracts were included the authors were contacted for further information. No relevant conference abstracts were identified for this guideline. Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

Type of Studies

Randomised trials, non-randomised trials, and observational studies (including diagnostic or prognostic studies) were included in the evidence reviews as appropriate.

For most intervention reviews in this guideline, parallel randomised controlled trials (RCTs) were included because they are considered the most robust type of study design that can produce an unbiased estimate of the intervention effects. If non-randomised studies were appropriate for inclusion (for example, non-drug trials with no randomised evidence) the GDG stated a priori in the protocol that either certain identified variables must be equivalent at baseline or else the analysis had to adjust for any baseline differences. If the study did not fulfil either criterion it was excluded. Please refer to the review protocols in Appendix C for full details on the study design of studies selected for each review question.

For diagnostic review questions, diagnostic RCTs, cross-sectional studies and retrospective studies were included. For prognostic review

questions, prospective and retrospective cohort studies were included. Case-control studies were not included.

Where data from observational studies were included, the results for each outcome were presented separately for each study and meta-analysis was not conducted.

Identifying and Analysing Evidence of Cost-effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical effectiveness and cost-effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost-effectiveness') rather than the total implementation cost. Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Health economic evidence was sought relating to the key clinical issues being addressed in the guideline. Health economists:

- Undertook a systematic review of the published economic literature
- Undertook new cost-effectiveness analysis in priority areas

Literature Review

The health economists:

- Identified potentially relevant studies for each review question from the health economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against prespecified inclusion and exclusion criteria to identify relevant studies (see below for details).

Inclusion and Exclusion Criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequences analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost- effectiveness without disaggregated costs and effects, were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded. Studies published before 1999 and studies from non-Organisation for Economic Co-operation and Development (non-OECD) countries or the USA were also excluded, on the basis that the applicability of such studies to the present UK NHS context is likely to be too low for them to be helpful for decision-making.

Remaining health economic studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a High quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. However, in this guideline, no economic studies were excluded on the basis that more applicable evidence was available.

For more details about the assessment of applicability and methodological quality see Table 7 in the full version of the guideline and the economic evaluation checklist (see Appendix G of the 2012 NICE guidelines manual) and the health economics review protocol (see Appendix D).

Number of Source Documents

See Appendix E: Clinical Article Selection and Appendix F: Economic Article Selection (see the "Availability of Companion Documents" field) for detailed flow charts on the article selection process, including total number of records identified through database searching, records screened, records excluded, full-text articles assessed for eligibility, studies included in review, and studies excluded from review.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Overall Quality of Outcome Evidence in Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Level	Description
High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Guideline Centre on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance and related appendices.

Identifying and Analysing Evidence of Effectiveness

After having identified potentially relevant studies for each review question and reviewing full papers against prespecified inclusion and exclusion criteria, research fellows conducted the following tasks:

- Critically appraised relevant studies using the appropriate study design checklist as specified in the NICE guidelines manual (see the "Availability of Companion Documents" field). Prognostic or qualitative studies were critically appraised using National Guideline Centre checklists.
- Extracted key information about interventional study methods and results using 'Evibase', National Guideline Centre's purpose-built software. Evibase produces summary evidence tables, including critical appraisal ratings. Key information about non-interventional study methods and results was manually extracted onto standard evidence tables and critically appraised separately (evidence tables are included in Appendix H).
- Generated summaries of the evidence by outcome. Outcome data were combined, analysed and reported according to study design:
    - Randomised data were meta-analysed where appropriate and reported in Grading of Recommendations Assessment, Development and Evaluation (GRADE) profile tables.
    - Observational data were presented as a range of values in GRADE profile tables or meta-analysed if appropriate.
    - Prognostic data were meta-analysed where appropriate and reported in GRADE profile tables.
    - Diagnostic data studies were meta-analysed where appropriate or presented as a range of values in adapted GRADE profile tables.
- A sample of a minimum of 10% of the abstract lists of the first 3 sifts by new reviewers were double-sifted by a senior research fellow. As no papers were missed by any reviewers, no further double-sifting was carried out. All of the evidence reviews were quality assured by a senior research fellow.

Methods of Combining Clinical Studies

Data Synthesis for Intervention Reviews

Where possible, meta-analyses were conducted using Cochrane Review Manager (RevMan5) software to combine the data given in all studies for each of the outcomes of interest for the review question.

For some questions stratification was used, and this is documented in the individual review question protocols (see Appendix C).

Analysis of Different Types of Data

See Section 4.3.3.1.1 of the full version of the guideline for details regarding analysis of different types of data including dichotomous outcomes,

continuous outcomes, generic inverse variance, heterogeneity, and complex analysis.

Data Synthesis for Prognostic Factor Reviews

Odds ratios (ORs), risk ratios (RRs), or hazard ratios (HRs), with their 95% confidence intervals (CIs), for the effect of the prespecified prognostic factors were extracted from the studies. Studies were only included if the confounders prespecified by the GDG were either matched at baseline or were adjusted for in multivariate analysis.

Studies of lower risk of bias were preferred, taking into account the analysis and the study design. In particular, prospective cohort studies were preferred if they reported multivariable analyses that adjusted for key confounders identified by the GDG at the protocol stage for that outcome. Data were not combined in meta-analyses for prognostic studies.

Data Synthesis for Diagnostic Test Accuracy Reviews

Two review protocols were produced to reflect the 2 different diagnostic study designs.

Diagnostic Randomised Controlled Trials (RCTs)

Diagnostic RCTs (sometimes referred to as test and treat trials) are a randomised comparison of 2 diagnostic tests, with study outcomes being clinically important consequences of the diagnosis (patient-related outcome measures similar to those in intervention trials, such as mortality). Patients are randomised to receive test A or test B, followed by identical therapeutic interventions based on the results of the test (so someone with a positive result would receive the same treatment regardless of whether they were diagnosed by test A or test B). Downstream patient outcomes are then compared between the 2 groups. As treatment is the same in both arms of the trial, any differences in patient outcomes will reflect the accuracy of the tests in correctly establishing who does and does not have the condition. Data were synthesised using the same methods as for intervention reviews (see Section 4.3.3.1.1 in the full version of the guideline).

Diagnostic Accuracy Studies

For diagnostic test accuracy studies, a positive result on the index test was found if the patient had values of the measured quantity above or below a threshold value, and different thresholds could be used. The thresholds were prespecified by the GDG including whether or not data could be pooled across a range of thresholds. Diagnostic test accuracy measures used in the analysis were: area under the receiver operating characteristics (ROC) curve (AUC), and, for different thresholds (if appropriate), sensitivity and specificity. The threshold of a diagnostic test is defined as the value at which the test can best differentiate between those with and without the target condition. In practice this varies amongst studies. If a test has a high sensitivity then very few people with the condition will be missed (few false negatives). Conversely, if a test has a high specificity then few people without the condition would be incorrectly diagnosed (few false positives). For this guideline, sensitivity was considered more important than specificity due to the consequences of a missed diagnosis of cirrhosis (false negative result).

Coupled forest plots of sensitivity and specificity with their 95% confidence intervals (CIs) across studies (at various thresholds) were produced for each test, using RevMan5. Diagnostic meta-analysis was conducted where appropriate, that is, when 3 or more studies were available per threshold. Test accuracy for the studies was pooled using the bivariate method for the direct estimation of summary sensitivity and specificity using a random effects approach in WinBUGS software.

Diagnostic meta-analysis was conducted where appropriate, that is, when 3 or more studies were available per threshold. Test accuracy for the studies was pooled using the bivariate method for the direct estimation of summary sensitivity and specificity using a random effects approach in WinBUGS software. The advantage of this approach is that it produces summary estimates of sensitivity and specificity that account for the correlation between the 2 statistics. Other advantages of this method have been described elsewhere. The bivariate method uses logistic regression on the true positives, true negatives, false positives and false negatives reported in the studies. Overall sensitivity and specificity and confidence regions were plotted (using methods outlined by Novielli 2010). Pooled sensitivity and specificity and their 95% CIs were reported in the clinical evidence summary tables. For thresholds with fewer than 3 studies, median sensitivity and the paired specificity were reported where possible.

Heterogeneity or inconsistency amongst studies was visually inspected in the forest plots.

Data Synthesis for Risk Prediction Rules

Evidence reviews on risk prediction rules or risk prediction tool results were presented separately for discrimination and calibration. The discrimination data were analysed according to the principles of data synthesis for diagnostic accuracy studies as outlined above. Calibration data such as r-squared (R^2), if reported, were presented separately to the discrimination data. The results were presented for each study separately along with the quality rating for the study.

Appraising the Quality of Evidence by Outcomes

Intervention Reviews

The evidence for outcomes from the included RCTs and, where appropriate, observational studies were evaluated and presented using an adaptation of the GRADE toolbox developed by the international GRADE working group (www.gradeworkinggroup.org). The software (GRADEpro) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results.

Each outcome was first examined for each of the quality elements listed and defined in Table 2 of the full guideline. Details of how the 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) were appraised for each outcome are given in Sections 4.3.4.1.1 to 4.3.4.1.4 in the full version of the guideline. Publication or other bias was only taken into consideration in the quality assessment if it was apparent.

Overall Grading of the Quality of Clinical Evidence

Once an outcome had been appraised for the main quality elements, an overall quality grade was calculated for that outcome. The scores (0, −1 or −2) from each of the main quality elements were summed to give a score that could be anything from 0 (the best possible) to −8 (the worst possible). However scores were capped at −3. This final score was then applied to the starting grade that had originally been applied to the outcome by default, based on study design. All RCTs started as High and the overall quality became Moderate, Low or Very Low if the overall score was −1, −2 or −3 points respectively. The significance of these overall ratings is explained in "Rating Scheme for the Strength of the Evidence" field. The reasons for downgrading in each case were specified in the footnotes of the GRADE tables.

Observational interventional studies started at Low, and so a score of −1 would be enough to take the grade to the lowest level of Very Low. Observational studies could, however, be upgraded if there were all of: a large magnitude of effect, a dose-response gradient, and if all plausible confounding would reduce the demonstrated effect.

See Section 4.3.4 for information on quality assessment of prognostic and diagnostic studies.

Assessing Clinical Importance

The GDG assessed the evidence by outcome in order to determine if there was, or potentially was, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, binary outcomes were converted into absolute risk differences (ARDs) using GRADEpro software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio.

The assessment of clinical benefit, harm, or no benefit or harm was based on the point estimate of absolute effect for intervention studies, which was standardised across the reviews. The GDG considered for most of the outcomes in the intervention reviews that if at least 100 participants per 1000 (10%) achieved the outcome of interest (for a positive outcome) in the intervention group compared to the comparison group then this intervention would be considered beneficial. The same point estimate but in the opposite direction applied if the outcome was negative. For adverse events 50 events or more per 1000 (5%) represented clinical harm. For continuous outcomes if the mean difference was greater than the minimally important difference (MID) then this resented a clinical benefit or harm. For critical outcomes such as mortality any reduction or increase was considered to be clinically important.

This assessment was carried out by the GDG for each critical outcome, and an evidence summary table was produced to compile the GDG's assessments of clinical importance per outcome, alongside the evidence quality and the uncertainty in the effect estimate (imprecision).

Clinical Evidence Statements

Clinical evidence statements are summary statements that are included in each review chapter, and which summarise the key features of the clinical effectiveness evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements are presented by outcome and encompass the following key features of the evidence:

- The number of studies and the number of participants for a particular outcome.
- An indication of the direction of clinical importance (if one treatment is beneficial or harmful compared to the other, or whether there is no difference between the 2 tested treatments).
- A description of the overall quality of the evidence (GRADE overall quality).

Identifying and Analysing Evidence of Cost-effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical effectiveness and cost-effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost-effectiveness') rather than the total implementation cost. Thus, if the evidence suggests that a strategy provides significant health benefits at an

acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Health economic evidence was sought relating to the key clinical issues being addressed in the guideline. The health economists:

- Undertook a systematic review of the economic literature.
- Undertook new cost-effectiveness analysis in priority areas.

Literature Review

The health economists:

- Critically appraised relevant studies using the economic evaluations checklist as specified in the NICE guidelines manual.
- Extracted key information about the studies' methods and results into evidence tables (included in Appendix I).
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter for each review question) – see below for details.

NICE Economic Evidence Profiles

NICE economic evidence profile tables were used to summarise cost and cost-effectiveness estimates for the included health economic studies in each review chapter. The economic evidence profile shows an assessment of applicability and methodological quality for each economic study, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from the NICE guidelines manual. It also shows the incremental costs, incremental effects (for example, quality-adjusted life years [QALYs]) and incremental cost-effectiveness ratio (ICER) for the base case analysis in the study, as well as information about the assessment of uncertainty in the analysis. See Table 7 in the full version of the guideline for more details.

When a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.

Undertaking New Health Economic Analysis

As well as reviewing the published health economic literature for each review question, new health economic analysis was undertaken by the health economist in selected areas. Priority areas for new analysis were agreed by the GDG after formation of the review questions and consideration of the existing health economic evidence.

The GDG identified the highest priority areas for original health economic modelling as:

- Risk factors for cirrhosis
- The appropriate tests (blood tests, non-invasive tests or a combination) for diagnosing cirrhosis
- Frequency of surveillance testing for the early detection of hepatocellular carcinoma
- Frequency of surveillance testing for the detection of oesophageal varices

This was due to the number of people affected by these questions and the current uncertainty as to what the most cost-effective solutions would be, due to the lack of published economic models encompassing the whole pathway of cirrhosis from diagnosis to end-stage liver disease. New work was therefore conducted, which entailed the development of the National Guideline Centre Liver Disease Pathway Model to address all of the questions prioritised for this guideline.

The following general principles were adhered to in developing the cost-effectiveness analysis:

- Methods were consistent with the NICE reference case for interventions with health outcomes in National Health Service (NHS) settings.
- The GDG was involved in the design of the model, selection of inputs and interpretation of the results.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data were not available GDG expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was peer-reviewed by another health economist at the National Guideline Centre.

Full methods for the cost-effectiveness analysis are described in Appendix N.

Cost-effectiveness Criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost-effective (given that the estimate

was considered plausible) if either of the following criteria applied:

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention cost less than £20,000 per QALY gained compared with the next best strategy

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter in the full version of the guideline, with reference to issues regarding the plausibility of the estimate or to the factors set out in 'Social value judgements: principles for the development of NICE guidance'.

When QALYs or life years gained are not used in the analysis, results are difficult to interpret unless one strategy dominates the others with respect to every relevant health outcome and cost.

In the Absence of Economic Evidence

When no relevant published health economic studies were found, and a new analysis was not prioritised, the GDG made a qualitative judgement about cost-effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the review of clinical effectiveness evidence.

The UK NHS costs reported in the guideline are those that were presented to the GDG and were correct at the time recommendations were drafted. They may have changed subsequently before the time of publication. However, the GDG has no reason to believe they have changed substantially.

Methods Used to Formulate the Recommendations

Expert Consensus

Informal Consensus

Description of Methods Used to Formulate the Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Guideline Centre on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance and related appendices.

This guidance was developed in accordance with the methods outlined in the National Institute for Health and Care Excellence (NICE) guidelines manual (the 2012 version was followed until consultation and 2014 version was followed from the start of consultation [see the "Availability of Companion Documents" field]). The process used to identify and review clinical evidence is summarised in Figure 1 of the full version of the guideline.

Who Developed This Guideline?

A multidisciplinary Guideline Development Group (GDG) comprising health professionals and researchers as well as lay members developed this guideline.

The group met approximately every 5 to 6 weeks during the development of the guideline.

Staff from the National Guideline Centre provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers (research fellows), health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

Developing Recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendices H and I.

- Summaries of clinical and economic evidence and quality (see Chapters 5–15 in the full version of the guideline)
- Forest plots (see Appendix K)
- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (see Appendix N)

Recommendations were drafted on the basis of the GDG's interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally in an economic model, or informally. Firstly, the net clinical benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. When this was done informally, the GDG took into account the clinical benefits and harms when one intervention was compared with another. The assessment of net clinical benefit was moderated by the importance placed on the outcomes (the GDG's values and preferences), and the confidence the GDG had in the evidence (evidence quality). Secondly, the GDG assessed whether the net clinical benefit justified any differences in costs between the alternative interventions.

When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on its expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs compared to the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through discussions in the GDG meeting. The GDG also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation.

The GDG considered the appropriate 'strength' of each recommendation. This takes into account the quality of the evidence but is conceptually different. Some recommendations are 'strong' in that the GDG believes that the vast majority of healthcare and other professionals and patients would choose a particular intervention if they considered the evidence in the same way that the GDG has. This is generally the case if the benefits clearly outweigh the harms for most people and the intervention is likely to be cost-effective. However, there is often a closer balance between benefits and harms, and some patients would not choose an intervention whereas others would. This may happen, for example, if some patients are particularly averse to some side effect and others are not. In these circumstances the recommendation is generally weaker, although it may be possible to make stronger recommendations about specific groups of patients (see the "Rating Scheme for the Strength of Recommendations" field).

The GDG focused on the following factors in agreeing the wording of the recommendations:

- The actions health professionals need to take
- The information readers need to know
- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weak recommendations)
- The involvement of patients (and their carers if needed) in decisions on treatment and care
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions

The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections within each chapter in the full version of the guideline.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group (GDG) makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the GDG is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

Interventions That Must (or Must Not) Be Used

The GDG usually uses 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally the GDG uses 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation

The GDG uses 'offer' (and similar words such as 'refer' or 'advise') when confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. The GDG uses similar forms of words (for example, 'Do not offer…') when confident that an intervention will not be of benefit for most patients.

Interventions That Could Be Used

The GDG uses 'consider' when confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Cost Analysis

See the "Economic Evidence" sections in the full version of the guideline (see the "Availability of Companion Documents" field) for specific cost-effectiveness considerations for each guideline review question.

Cost-effectiveness Analysis: Diagnostic Tests and Surveillance Strategies for Cirrhosis

Refer to Appendix N in the full guideline appendices (see the "Availability of Companion Documents" field) for cost-effectiveness analyses on the following topics:

- An original cost-utility analysis that compared 6 strategies to diagnose cirrhosis in people with non-alcoholic fatty liver disease (NAFLD) and advanced fibrosis with a retest frequency of 2 years
- An original cost-utility analysis that compared 6 strategies to diagnose cirrhosis in people with alcoholic liver disease (ALD), with a retest frequency of 2 years
- An original cost-utility analysis that compared 7 strategies to diagnose cirrhosis in people with hepatitis B and hepatitis B e-antigen (HBeAg) negative with a retest frequency of 2 years
- An original cost-utility analysis that compared 7 strategies to diagnose cirrhosis in people with hepatitis B and HBeAg positive with a retest frequency of 2 years
- An original cost-utility analysis that compared 20 strategies to diagnose cirrhosis in people with hepatitis C with a retest frequency of 2 years
- An original cost-utility analysis that compared 6-monthly with annual surveillance for hepatocellular carcinoma (HCC) in people with cirrhosis at a cost-effectiveness threshold of £20,000 per quality-adjusted life-year (QALY) gained
- An original cost-utility analysis that compared annual, 2-yearly and 3-yearly surveillance for the detection of varices in people with cirrhosis at a cost-effectiveness threshold of £20,000 per QALY gained

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the National Institute for Health and Care Excellence (NICE) Web site.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

Refer to "Type of Studies" in the "Description of Methods Used to Collect/Select the Evidence" field.

Also refer to "Evidence Statements" sections in the full version of the guideline for discussion of the evidence supporting each review question.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Better recognition of individuals at risk of cirrhosis would allow for more timely intervention.
- Early intervention to stabilise disease progression helps avoid or delay clinical decompensation and the need for liver transplantation.
- Prophylactic treatment of oesophageal varices prevents variceal haemorrhage, and the use of antibiotics is important for the primary prevention of spontaneous bacterial peritonitis.

See also the "Trade-off between clinical benefits and harms" sections in the full version of the guideline (see the "Availability of Companion Documents" field) for benefits of specific interventions.

Potential Harms

- Adverse events of antibiotics include diarrhoea, flatulence, abdominal pain, nausea, gastrointestinal bleeding, renal failure, and the development of antibiotic resistance.
- The invasive nature of liver biopsy means that it causes adverse events, including a small risk of death. It is also considered unpleasant by patients, leading to a very low acceptability among patients.

See also the "Trade-off between clinical benefits and harms" sections in the full version of the guideline (see the "Availability of Companion Documents" field) for additional detail on harms of specific interventions.

Qualifying Statements

Qualifying Statements

- The recommendations in this guideline represent the view of the National Institute for Health and Care Excellence (NICE), arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The application of the recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.
- Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.
- The causes of cirrhosis in children and young people are generally different from those in adults (for example, biliary atresia), and the diagnosis and management of these conditions is different. However, the recommendations may be useful to clinicians who are caring for young people who transition into this care pathway when they reach 16.

Implementation of the Guideline

Description of Implementation Strategy

Putting This Guideline into Practice

The National Institute for Health and Care Excellence (NICE) has produced tools and resources to help put this guideline into practice.

Putting recommendations into practice can take time. How long may vary from guideline to guideline, and depends on how much change in

practice or services is needed. Implementing change is most effective when aligned with local priorities.

Changes recommended for clinical practice that can be done quickly – like changes in prescribing practice – should be shared quickly. This is because healthcare professionals should use guidelines to guide their work – as is required by professional regulating bodies such as the General Medical and Nursing and Midwifery Councils.

Changes should be implemented as soon as possible, unless there is a good reason for not doing so (for example, if it would be better value for money if a package of recommendations were all implemented at once).

Different organisations may need different approaches to implementation, depending on their size and function. Sometimes individual practitioners may be able to respond to recommendations to improve their practice more quickly than large organisations.

Here are some pointers to help organisations put NICE guidelines into practice:

1. Raise awareness through routine communication channels, such as email or newsletters, regular meetings, internal staff briefings and other communications with all relevant partner organisations. Identify things staff can include in their own practice straight away.
2. Identify a lead with an interest in the topic to champion the guideline and motivate others to support its use and make service changes, and to find out any significant issues locally.
3. Carry out a baseline assessment against the recommendations to find out whether there are gaps in current service provision.
4. Think about what data you need to measure improvement and plan how you will collect it. You may want to work with other health and social care organisations and specialist groups to compare current practice with the recommendations. This may also help identify local issues that will slow or prevent implementation.
5. Develop an action plan, with the steps needed to put the guideline into practice, and make sure it is ready as soon as possible. Big, complex changes may take longer to implement, but some may be quick and easy to do. An action plan will help in both cases.
6. For very big changes include milestones and a business case, which will set out additional costs, savings and possible areas for disinvestment. A small project group could develop the action plan. The group might include the guideline champion, a senior organisational sponsor, staff involved in the associated services, finance and information professionals.
7. Implement the action plan with oversight from the lead and the project group. Big projects may also need project management support.
8. Review and monitor how well the guideline is being implemented through the project group. Share progress with those involved in making improvements, as well as relevant boards and local partners.

NICE provides a comprehensive programme of support and resources to maximise uptake and use of evidence and guidance. See the into practice pages for more information.

Also see Leng G, Moore V, Abraham S, editors (2014) Achieving high quality care – practical experience from NICE. Chichester: Wiley.

Implementation Tools

Clinical Algorithm

Foreign Language Translations

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Guideline Centre. Cirrhosis in over 16s: assessment and management. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jul 6. 14 p. (NICE guideline; no. 50).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

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Guideline Developer(s)

National Guideline Centre - National Government Agency [Non-U.S.]

Source(s) of Funding

The National Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on this guideline.

Guideline Committee

Guideline Development Group

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Financial Disclosures/Conflicts of Interest

At the start of the guideline development process all Guideline Development Group (GDG) members declared interests including consultancies,

fee-paid work, shareholdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B in the full guideline appendices.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download in ePub or eBook formats from the NICE Web site .

Availability of Companion Documents

he following are available:

- Cirrhosis in over 16s: assessment and management. Full guideline. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jul. 303 p. (NICE guideline; no. 50). Available from the National Institute for Health and Care Excellence (NICE) Web site .
- Cirrhosis in over 16s: assessment and management. Appendices A-H. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jul. 351 p. (NICE guideline; no. 50). Available from the NICE Web site .
- Cirrhosis in over 16s: assessment and management. Appendices I-Q. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jul. 283 p. (NICE guideline; no. 50). Available from the NICE Web site .
- Cirrhosis in over 16s: assessment and management. Baseline assessment tool. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jul. (NICE guideline; no. 50). Available from the NICE Web site .
- Cirrhosis in over 16s: assessment and management. Resource impact report. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jul. 16 p. (NICE guideline; no. 50). Available from the NICE Web site .
- Cirrhosis in over 16s: assessment and management. Resource impact template. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jul. (NICE guideline; no. 50). Available from the NICE Web site .
- The guidelines manual 2012. London (UK): National Institute for Health and Care Excellence (NICE); 2012 Nov. Available from the NICE Web site .
- Developing NICE guidelines: the manual 2014. London (UK): National Institute for Health and Care Excellence; 2014 Oct. Available from the NICE Web site .

Patient Resources

The following is available:

- Cirrhosis in over 16s: assessment and management. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jul. 6 p. Available in English and Welsh from the National Institute for Health and Care Excellence (NICE) Web site. Also available for download in ePub or eBook formats from the NICE Web site .

NGC Status

This NGC summary was completed by ECRI Institute on November 23, 2016.

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